WHAT IS CLAIMED IS:

1. An isolated peptide comprising a sequence of at least four amino acids defined by formula P_2P_1--$P_1'P_2'$ wherein

P_2 is a charged amino acid, a polar amino acid, or an aliphatic amino acid but is not an aromatic amino acid;

P_1 is an aromatic amino acid or an aliphatic amino acid but not a polar amino acid or a charged amino acid;

P_1' is a charged amino acid, or aliphatic amino acid, or a polar amino acid but is not an aromatic amino acid;

P_2' is an uncharged aliphatic polar amino acid or an aromatic amino acid; and

wherein said peptide is cleaved between P_1 and P_1' by a human aspartyl protease encoded by the nucleic acid sequence of SEQ ID NO:1 or SEQ ID NO:3 and said peptide does not comprise the corresponding P_2P_1--$P_1'P_2'$ portion of amino acid sequences depicted in SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:31; SEQ ID NO:32; SEQ ID NO:33; SEQ ID NO:34; SEQ ID NO:35; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:39; or SEQ ID NO:40.

2. The isolated peptide of claim 1, comprising an amino acid sequence defined by formula P_2P_1--$P_1'P_2'P_3'$, wherein P_3' is any amino acid, and wherein said peptide does not comprise the corresponding P_2P_1--$P_1'P_2'P_3'$ portion of amino acid sequences depicted in SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:31; SEQ ID NO:32; SEQ ID NO:33; SEQ ID NO:34; SEQ ID NO:35; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:39; or SEQ ID NO:40.

3. The isolated peptide of claim 1, comprising an amino acid sequence defined by formula $P_3P_2P_1$--$P_1'P_2'P_3'$, wherein P_3 is an uncharged polar amino acid, an uncharged aliphatic amino acid, or an aromatic amino acid, and wherein said said peptide does not comprise the corresponding $P_3P_2P_1$--$P_1'P_2'P_3'$ portion of amino acid sequences depicted in SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:31; SEQ ID NO:32; SEQ ID NO:33; SEQ ID NO:34; SEQ ID NO:35; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:39; or SEQ ID NO:40.

4. The isolated peptide of claim 3, comprising an amino acid sequence defined by formula $P_4P_3P_2P_1$--$P_1'P_2'P_3'$, wherein said P_4 is a charged amino acid, a polar amino acid or an aliphatic amino acid but not an aromatic amino acid and said peptide does not comprise the corresponding $P_4P_3P_2P_1$--$P_1'P_2'P_3'$ portion of amino acid sequences depicted in SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:31; SEQ ID NO:32; SEQ ID NO:33; SEQ ID NO:34; SEQ ID NO:35; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:39; or SEQ ID NO:40.

5. The isolated peptide of any one of claims 2 through 4, further comprising an amino acid at position P_4' immediately to the carboxy-terminal position of P_3' wherein said P_4' is any amino acid said, and wherein the peptide does not comprise the corresponding $P_3P_2P_1$--$P_1'P_2'P_3'$ P_4' portion of amino acid sequences depicted in SEQ ID NO:19; SEQ ID NO:20; SEQ ID NO:21; SEQ ID NO:26; SEQ ID NO:27; SEQ ID NO:28; SEQ ID NO:31; SEQ ID NO:32; SEQ ID NO:33; SEQ ID NO:34; SEQ ID NO:35; SEQ ID NO:36; SEQ ID NO:37; SEQ ID NO:38; SEQ ID NO:39; or SEQ ID NO:40.

6. The isolated peptide of claim 1, wherein said P_2 is an amino acid selected from the group consisting of N, L, K, S, G, T, D, A, Q and E.

7. The isolated peptide of claim 1, wherein said P_1 is an amino acid selected from the group consisting of Y, L, M, Nle, F, and H.

8. The isolated peptide of claim 1, wherein said P_1' is an amino acid selected from the group consisting of E, A, D, M, Q, S and G.

9. The isolated peptide of claim 1, wherein said P_2' is an amino acid selected from the group consisting of V, A, N, T, L, F, and S.

10. The isolated peptide of claim 2, wherein said P_3' is an amino acid selected from the group consisting of E, G, F, H, cysteic acid and S.

11. The isolated peptide of claim 3, wherein said P_3 is an amino acid selected from the group consisting of A, V, I, S, H, Y, T and F.

12. The isolated peptide of claim 4, wherein said P_4 is an amino acid selected from the group consisting of E, G, I, D, T, cysteic acid and S.

13. The isolated peptide of any one of claims 4-12, wherein said P_4' is an amino acid selected from the group consisting of F, W, G, A, H, P, G, N, S, and E.

14. The isolated peptide of any one of claims 1 through13 further comprising a first label.

15. The isolated peptide of claim 14 further comprising a second label.

16. An isolated peptide according to any one of claims 1-13, further comprising a detectable label and a quenching moiety, wherein cleavage of the peptide between P_1 and P_1' separate the quenching moiety from the label to permit detection of the label.

17. The isolated peptide of claim 10 or 12, wherein said cysteic acid further comprises a covalently attached label.

18. The isolated peptide of any one of claims 1-17, wherein the rate of cleavage of said peptide by said human aspartyl protease is greater than the rate of cleavage of a polypeptide comprising the human APP β-secretase cleavage sequence: SEVKM-DAEFR (SEQ ID NO:20).

19. The isolated peptide of any one of claims 1-17, wherein the rate of cleavage of said peptide by said human aspartyl protease is greater than the rate of cleavage of a polypeptide comprising the human APP Swedish KM→NL mutation, β-secretase cleavage sequence SEVNL-DAEFR (SEQ ID NO:19).

20. The isolated peptide of claim 1, wherein said peptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:5; SEQ ID NO:6; SEQ ID NO:7; SEQ ID NO:8; SEQ ID NO:9; SEQ ID NO:10; SEQ ID NO:11; SEQ ID NO:12; SEQ ID NO:13; SEQ ID NO:14; SEQ ID NO:15; SEQ ID NO:16; SEQ ID NO:17, SEQ ID NO:18; SEQ ID NO:120; SEQ ID NO:133; SEQ ID NO:134; SEQ ID NO:135; SEQ ID NO:136; SEQ ID NO:137; SEQ ID NO:138; SEQ ID NO:141; SEQ ID NO:143; SEQ ID NO:144; SEQ ID NO:145; SEQ ID NO:147; SEQ ID NO:148; SEQ ID NO:149; SEQ ID NO:150; SEQ ID NO:151; SEQ ID NO:152; SEQ ID NO:153; SEQ ID NO:154; SEQ ID NO:155; SEQ ID NO:156; SEQ ID NO:157; SEQ ID NO:158; SEQ ID NO:159; SEQ ID NO:160; SEQ ID NO:161; SEQ ID NO:162; SEQ ID NO:163; SEQ ID NO:164; SEQ ID NO:165; SEQ ID NO:166; SEQ ID NO:167; SEQ ID NO:168; SEQ ID NO:169; SEQ ID NO:190; SEQ ID NO:191; SEQ ID NO:192 and SEQ ID NO:193.

21. An isolated peptide comprising a sequence of at least four amino acids

defined by formula P_2P_1--$P_1'P_2'$, wherein:

P_2 comprises an amino acid selected from the group consisting of N, S, and D;

P_1 comprises an amino acid selected from the group consisting of Y, L, and Nle;

P_1' comprises an amino acid selected from the group consisting of E, A, and D;

P_2' comprises an amino acid selected from the group consisting of A and V; and

wherein a human Aspartyl protease encoded by the nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO: 3 (Hu-Asp2) cleaves said peptide between P_1 and P_1';

with the proviso that if $P_1'P_2'$ comprise the sequence DA, P_2P_1 do not comprise the sequences NL or NNle.

22. An isolated peptide according to claim 21, wherein the peptide amino acid sequence consists of 4-50 amino acids.

23. An isolated peptide according to claim 21, wherein the Hu-Asp2 cleaves the peptide at a rate greater than the Hu-Asp2 cleaves a corresponding peptide having the P_2P_1--$P_1'P_2'$ amino acid sequence KMDA.

24. An isolated peptide according to claim 21, wherein the Hu-Asp2 cleaves the peptide at a rate greater than the Hu-Asp2 cleaves a corresponding peptide having the P_2P_1--$P_1'P_2'$ amino acid sequence KMDA.

25. A peptide according to claim 21, further comprising a label.

26. A peptide according to claim 21, further comprising a label and a quenching moiety that quenches the label, wherein the label and quenching moiety are

attached on opposite sides of the P_1--P_1 peptide bind, whereby cleavage of the P_1--P_1 peptide bond separates the label and quenching moiety.

27. A polypeptide comprising a peptide sequence according to claim 21, and further comprising a transmembrane domain to localize the polypeptide to a cellular membrane when the polypeptide is expressed in a eukaryotic cell.

28. A polypeptide comprising a peptide according to any one of claims 1 through 20 and further comprising a transmembrane domain amino acid sequence.

29. A polypeptide according to claim 28, wherein the peptide is N-terminal to the transmembrane domain.

30. The polypeptide of claim 28 or 29, wherein the peptide and the transmembrane domain are separated by a linker.

31. The polypeptide of claim 30, wherein said linker is a peptide linker comprising between about 20 to about 40 amino acids.

32. The polypeptide according to any one of claims 28-31, wherein said transmembrane domain anchors said polypeptide to an intracellular membrane selected from the group consisting of the Golgi or the endoplasmic reticulum.

33. The fusion protein of any of claims 28-32, wherein said transmembrane domain is selected from the group consisting of the transmembrane domain of galactosyltransferase, the transmembrane domain of sialyly transferase; the transmembrane domain of human aspartyl transferase 1; the transmembrane domain of human aspartyl transferase 2; the transmembrane

domain of syntaxin 6; the transmembrane domain of ubiquitin; the transmembrane domain of insulin B chain and the transmembrane domain of APP.

34. The polypeptide according to any one of claims 28-32, further comprising a reporter protein amino acid sequence.

35. The polypeptide of claim 34, wherein said reporter protein is selected from the group consisting of luciferase; alkaline phosphatase; β-galactosidase; β-glucorinidase; green fluorescent protein; chloramphenical acetyl transferase;

36. A polynucleotide comprising a nucleotide sequence that encodes a polypeptide according to any one of claims 20-35.

37. A polynucleotide comprising a nucleotide sequence that encodes a peptide according to any one of claims 1-27.

38. A vector comprising a polynucleotide according to claim 36.

39. A vector comprising a polynucleotide according to claim 37.

40. A vector according to claim 38 wherein said polynucleotide is operably linked to a promoter to promote expression of the fusion protein encoded by the polynucleotide in a host cell.

41. A host cell transformed or transfected with a polynucleotide according to claim 36.

42. A host cell transformed or transfected with a vector according to any one of claims 38-40.

43. A method for assaying for modulators of β-secretase activity, comprising the steps of:

(a) contacting a first composition with a second composition both in the presence and in the absence of a putative modulator compound, wherein the first composition comprises a mammalian β-secretase polypeptide or biologically active fragment thereof, and wherein the second composition comprises a substrate, wherein said substrate comprises a peptide according to any of claims 1 through 26 or a polypeptide according to any of claims 27-35;

(b) measuring cleavage of the substrate peptide in the presence and in the absence of the putative modulator compound; and

(c) identifying modulators of β-secretase activity from a difference in cleavage in the presence versus in the absence of the putative modulator compound, wherein a modulator that is a β-secretase antagonist reduces such cleavage and a modulator that is a β-secretase agonist increases such cleavage.

44. The method of claim 43, wherein said first composition comprises a purified human Asp2 polypeptide.

45. The method of claim 43, wherein said first composition comprises a soluble fragment of a human Asp2 polypeptide that retains Asp2 β-secretase activity.

46. The method of claim 45, wherein said soluble fragment is a fragment lacking an Asp2 transmembrane domain.

47. A method according to claim 43, wherein the β-secretase polypeptide of the first composition comprises a polypeptide purified and isolated from a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the β-secretase polypeptide.

48 A method according to claim 43, wherein the polypeptide of the first composition is expressed in a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the polypeptide, and wherein the measuring step comprises measuring APP processing activity of the cell.

49. The method claim of any of claims 43-48, further comprising a step of treating Alzheimer's Disease with an agent identified as an inhibitor of Hu-Asp2.

50. A β-secretase modulator identified according to the method of any of claims 43-48.

51. A method of inhibiting β-secretase activity *in vivo* comprising a step of administering a modulator according to claim 50 that is a β-secretase antagonist to a mammal in an amount effective to inhibit β-secretase in cells of said mammal.

52. A method of producing a substrate for a β-secretase assay comprising:
growing a host cell transformed or transfected with a vector of claim 40 in a manner allowing expression of said polypeptide.

53. The method of claim 52, further comprising purifying said polypeptide.

54. The method of claim 52, wherein said host cell is selected from the group consisting of a mammalian host cell, a bacterial host cell and a yeast host cell.

55. A pharmaceutical composition comprising a modulator of claim 50 and a pharmaceutically acceptable carrier.

56. A method of treating a disease or condition characterized by an abnormal β-secretase activity comprising administering to a subject in need of treatment a pharmaceutical composition of claim 55.

57. A use of a modulator identified according to the method claim 43 in the manufacture of a medicament for the treatment of Alzheimer's Disease.

58. A method for identifying agents that inhibit the activity of human Asp2 aspartyl protease (Hu-Asp2), comprising the steps of:

(a) contacting a peptide of any of claims 1 through 26 or a polypeptide of any of claims 27-35 and a composition comprising an Hu-Asp2 activity in the presence and absence of a test agent;

(b) determining the cleavage of said peptide or polypeptide between said P_1 and P_1' by said Hu-Asp2 in the presence and absence of the test agent; and

(c) comparing said cleavage activity of the Hu-Asp2 in the presence of the test agent to the activity in the absence of the test agent to identify an agent that inhibits said cleavage by the Hu-Asp2, wherein reduced activity in the presence of the test agent identifies an agent that inhibits Hu-Asp2 activity.

59. A method according to claim 58, wherein the Hu-Asp2 is a recombinant Hu-Asp2 purified and isolated from a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes Hu-Asp2.

60. A method according to claim 58,

wherein the Hu-Asp2 is expressed in a cell, wherein the contacting comprises growing the cell in the presence and absence of the test agent, and

wherein the determining step comprises measuring cleavage of said peptide or fusion protein.

61. A method according to claim 60, wherein the cell further comprises a polynucleotide encoding the polypeptide, and wherein the contacting step comprises growing the cell under conditions in which the cell expresses the polypeptide.

62. A method according to claim 60 or 61, wherein the cell is a human embryonic kidney cell line 293 cell.

63. A method according to any one of claims 59-62 wherein the nucleotide sequence is selected from the group consisting of:

(a) a nucleotide sequence encoding the Hu-Asp2(a) amino acid sequence set forth in SEQ ID NO: 2;

(b) a nucleotide sequence encoding the Hu-Asp2(b) amino acid sequence set forth in SEQ ID NO: 4;

(c) a nucleotide sequence encoding a fragment of Hu-Asp2(a) (SEQ ID NO: 2) or Hu-Asp2(b) (SEQ ID NO: 4), wherein said fragment exhibits aspartyl protease activity characteristic of Hu-Asp2(a) or Hu-Asp2(b); and

(d) a nucleotide sequence of a polynucleotide that hybridizes under stringent hybridization conditions to a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 3.

64. A method for identifying agents that modulate the activity of Asp2 aspartyl protease, comprising the steps of:

(a) contacting an Asp2 aspartyl protease and a peptide of any of claims 1 through 26 or a polypeptide of any of claims 27 through 35 in the

presence and absence of a test agent, wherein the Asp2 aspartyl protease is encoded by a nucleic acid molecule that hybridizes under stringent hybridization conditions to a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 3;

(b) determining the cleavage of said peptide or fusion protein between said P_1 and said P_1' site by said Asp2 in the presence and absence of the test agent; and

(c) comparing the cleavage activity of said Asp2 in the presence of the test agent to the cleavage activity in the absence of the agent to identify agents that modulate the activity of the polypeptide, wherein a modulator that is an Asp2 inhibitor reduces said cleavage and a modulator that is an Asp2 agonist increases said cleavage.

65. A method according to 58 or 64, further comprising a step of treating Alzheimer's Disease with an agent identified as an inhibitor of Hu-Asp2.

67. A method for identifying agents that inhibit the activity of human Asp2 aspartyl protease (Hu-Asp2), comprising the steps of:

(a) growing a cell in the presence and absence of a test agent, wherein the cell expresses an Hu-Asp2 and expresses a protein comprising a peptide of any of claims 1 through 26 or a polypeptide of any of claims 27 through 35;

(b) determining the determining the cleavage of said protein at the site between said P_1 and P_1' in said cell in the presence and absence of the test agent; and

(c) comparing said cleavage activity in the presence of the test agent to the cleavage activity in the absence of the test agent to identify an agent that inhibits the activity of Hu-Asp2, wherein reduced cleavage activity in the presence of the test

agent identifies an agent that inhibits Hu-Asp2 activity.

68. A method according to claim 67, wherein the host cell has been transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes a Hu-Asp2, wherein said nucleotide sequence is selected from the group consisting of:

(a) a nucleotide sequence encoding the Hu-Asp2(a) amino acid sequence set forth in SEQ ID NO: 2;

(b) a nucleotide sequence encoding the Hu-Asp2(b) amino acid sequence set forth in SEQ ID NO: 4;

(c) a nucleotide sequence encoding a fragment of Hu-Asp2(a) (SEQ ID NO: 2) or Hu-Asp2(b) (SEQ ID NO: 4), wherein said fragment exhibits aspartyl protease activity characteristic of Hu-Asp2(a) or Hu-Asp2(b); and

(d) a nucleotide sequence of a polynucleotide that hybridizes under stringent hybridization conditions to a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 3.

68. A method according to any one of claims 66-67, further comprising a step of treating Alzheimer's Disease with an agent identified as an inhibitor of Hu-Asp2 according to steps (a)-(c).

69. The use of an agent identified as an inhibitor of Hu-Asp2 according to any one of claims 66-67 in the manufacture of a medicament for the treatment of Alzheimer's Disease.

70. A kit for performing a β-secretase assay comprising a β-secretase substrate comprising a peptide according to any of claims 1 through 27 and a β-secretase enzyme.

71. The kit of claim 70, wherein said β-secretase substrate is a polypeptide according to any of claims 28-35.

72. The kit of claim 70 or 71, further comprising reagents for detecting the cleavage of said peptide or fusion protein.

73. An isolated peptide comprising a sequence of at least 10 amino acids having the sequence SEISY-EVEFR (SEQ ID NO:152).

74. The isolated peptide of claim 73, wherein said peptide comprises at least 3 amino acids immediately to the carboxy-terminal of SEISY-EVEFR (SEQ ID NO:152).

75. The isolated peptide of claim 73, wherein said peptide comprises at least 3 amino acids immediately to the amino-terminal of SEISY-EVEFR (SEQ ID NO:152).

76. The isolated peptide of claim 73, wherein said peptide comprises at least 5 amino immediately to the carboxy-terminal of SEISY-EVEFR (SEQ ID NO:152).

77. The isolated peptide of claim 73, wherein said peptide comprises at least 5 amino immediately to the amino-terminal of SEISY-EVEFR (SEQ ID NO:152).

78. The isolated peptide of claim 73, wherein said peptide comprises at least 10 amino immediately to the amino-terminal of SEISY-EVEFR (SEQ ID NO:152).

79. The isolated peptide of claim 73, wherein said peptide comprises at least 13 amino acids.

80. The isolated peptide of claim 73, wherein said peptide comprises at least 15 amino acids.

81. The isolated peptide of claim 73, wherein said peptide comprises at least 20 amino acids.

82. The isolated peptide of claim 73, wherein said peptide comprises at least 50 amino acids.